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Studies on the synthesis and some reactions of (*S*)-proline hydrazides[1]

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Abstract

A convenient synthesis of (*S*)-proline hydrazide **2a** via the reaction of ethyl (*S*)-*N*-benzylprolinate with hydrazine hydrate and subsequent deprotection of (*S*)-*N*-benzyl proline hydrazide **5** is described. The latter, in methanolic solution, reacted with aromatic aldehydes as well as with cycloaliphatic ketones at room temperature to give the corresponding hydrazones of type **7** in good yields. The structure of the product with furan carbaldehyde **7b**, proving the (*E*)-configuration of the hydrazone, was established by X-ray crystallography. In the case of the unprotected (*S*)-proline hydrazide **2a**, the analogous reaction with aromatic aldehydes led to the expected hydrazones **7** or the 1*H*-pyrrolo[1,2-*c*]imidazol-1-one derivatives **8**, depending on the reaction conditions. The latter is formed via a secondary cyclocondensation of the initially formed **7** with a second molecule of the aldehyde. Whereas the reaction of (*S*)-*N*-benzyl proline hydrazide **5** with butyl isocyanate and isothiocyanate gave the corresponding semicarbazide and thiosemicarbazide, respectively, of type **9**, the unprotected (*S*)-proline hydrazide **2a** yielded the 1:2 adducts **10**. Thiosemicarbazide **9b** underwent cyclization reactions under basic (NaOH) and acidic (H_2SO_4) conditions to yield (*S*)-prolinyl-substituted 1,2,4-triazole-3-thione **11** and 1,3,4-thiadiazole-2-amine **12**, respectively.

1. Introduction

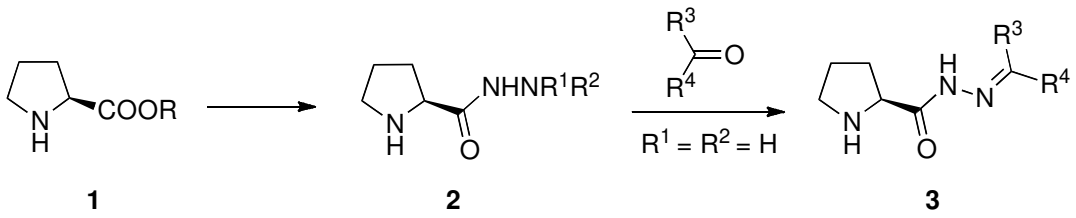
It is well documented that enantiopure (*S*)-proline **1a** (R = H) and its derivatives belong to privileged compounds widely applied in the field of asymmetric synthesis and organocatalysis.[2] On the other hand, carbohydrazides form an important class of building blocks for the preparation of diverse N-heterocycles[3] with practical applications as agrochemicals and pharmaceuticals.[4] Moreover, a variety of hydrazones derived from hydrazides are known for their biological activities.[5] Finally, also some hydrazides are used as pharmaceuticals, and isoniazid (isonicotinohydrazide), synthesized for the first time at the beginning of the 20th century, is the best known example of this class of compounds.[6]

Whereas proline amides and thioamides are rather well known and have been explored successfully as catalyst and ligands,[7] the related proline hydrazides **2** are less known. To the best of our knowledge, hydrazides of the non-protected (*S*)-proline are described only scarcely. The syntheses of (*S*)-pyroline hydrazide **2a** (R^1 = R^2 = H) by using anhydrous (absolute) hydrazine, as well as some of its hydrazones **3** (Scheme 1), were published in 1993.[8a] Interestingly, in another paper, the authors reported the formation of bicyclic 1:2 products, i.e., 2,3-disubstituted 1,3-diazabicyclo[3.3.0]octan-4-ones.[8b]

Treatment of (*S*)-proline with hydrazine hydrate in large excess at elevated temperature led to 4-amino-3,5-bis(2-pyrrolidine)-1,2,4-triazoles,[9] and proline hydrazide **2a** was proposed as key intermediate in the reaction. A biologically active hydrazone derived from proline hydrazide was prepared by using 2-chloroacetophenone.[10] In a very recent report, proline hydrazide prepared from methyl (*S*)-prolinate hydrochloride and excess hydrazine hydrate in methanolic solution was isolated and fully characterized.[11] The formed hydrazine hydrochloride was removed from the crude product via precipitation from methanol. In a recent study, the preparation of N'-mono- and N',N'-disubstituted (*S*)-proline hydrazides and their application as catalysts for asymmetric aldol reactions is reported.[12]

Due to our current interest in the synthesis and applications of heterocyclic carbohydrazides[13] as well as asymmetric synthesis,[14] we report now a convenient and efficient protocol for the preparation of (*S*)-proline hydrazide **2a**, which is a promising reagent for further, diverse applications.

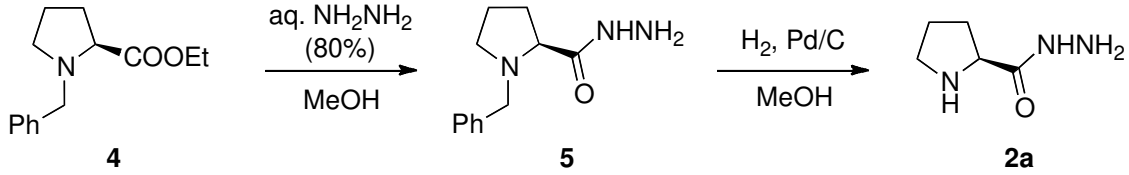
Scheme 1



2. Results and discussion

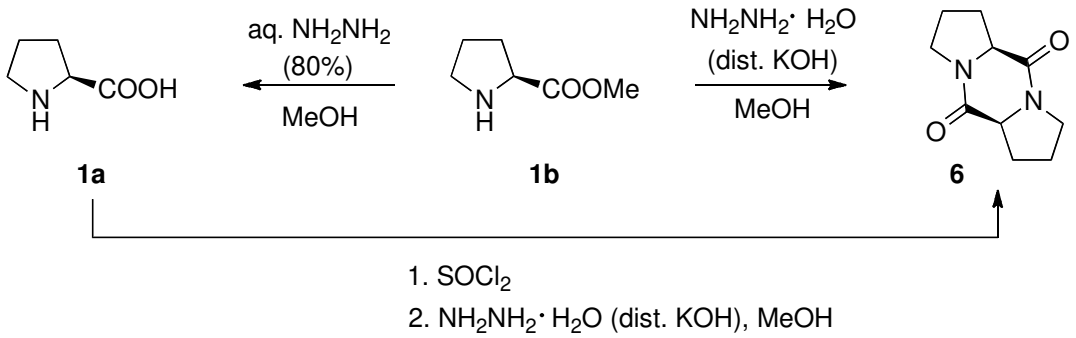
A typical procedure for the synthesis of acid hydrazides is the treatment of the corresponding esters with hydrazine hydrate.[15] Using this method, ethyl (*S*)-*N*-benzyl prolinate **4** can easily be transformed into (*S*)-*N*-benzyl proline hydrazide **5** in high yield (Scheme 2, see ref.[16]).

Scheme 2



In our hands, the reaction of methyl (*S*)-prolinate **1b** with a commercial aqueous solution of hydrazine (80%), carried out at room temperature, resulted in its hydrolysis, and proline **1a** was isolated as the sole product. Following the protocol reported in ref.[11], we obtained **2a** contaminated with hydrazine hydrochloride, which could not be removed completely by repeated treatment with methanol. On the other hand, when the aqueous hydrazine solution was distilled over KOH pellets and then used for the reaction with **1b**, a crystalline product was obtained, which was identified as the well known diketopiperazine derivative **6** (Scheme 3).[12] In another experiment, the sequential treatment of **1a** with thionyl chloride and hydrazine hydrate also led to **6**. Most likely, in both cases, hydrazine hydrate only acted as a base.

Scheme 3



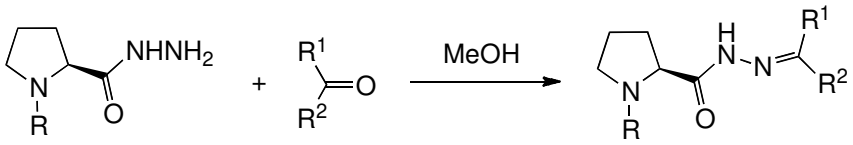
Having in hand the *N*-benzylated hydrazide **5**, the non-protected **2a** was prepared by standard hydrogenolysis over palladium on charcoal. Alternatively, substrate **5** was converted into **2a** using ammonium formate in boiling methanolic solution, in the presence of Pd/C as a deprotecting reagent. The physicochemical and spectroscopic properties of **2a** fitted well with the data reported in the literature.[8a,11] Thus, the method presented in Scheme 2 opens a convenient access to pure **2a** on a multigram scale.

In the second part of the study, selected reactions with hydrazides **2a** and **5** were performed using aldehydes, ketones, butyl isocyanate, and butyl isothiocyanate. The N-benzylated proline hydrazide **5** reacted smoothly with aldehydes at room temperature yielding the expected hydrazones **7** as a single isomer in each case (Scheme 4). The ^{1}H-NMR spectra showed that a single isomer is also present in solution. In the case of the non-protected proline hydrazide **2a**, the reaction course was dependent on the applied protocol and a test reaction was carried out with 4-methoxybenzaldehyde. Whereas slow addition of the aldehyde to a stirred solution of **2a** at room temperature led to the expected hydrazone **7e**, the reversed addition of both reagents (**2a** was added in small portions to a stirred solution of excess aldehyde) resulted in exclusive formation of the corresponding 1:2 product of type **8** in a diastereoselective manner (Scheme 5). Surprisingly, in two earlier publications,[8a,8b] both types of products, i.e. hydrazones **7** and 1:2 products **8**, were obtained using the same protocol based on addition of the corresponding aldehyde in one portion to the solution of **2a** at room temperature. In our hands, upon application of this protocol, formation of both products in a ratio of ca. 1:1 was observed.

It is worth mentioning that, in contrast to hydrazones **7a–d**, the non-protected analogues **7e–i** exist in solution as mixtures of two stereoisomers or conformers (^{1}H-NMR evidence). On the basis of the present data, it is not possible to formulate a convincing explanation of this phenomenon.

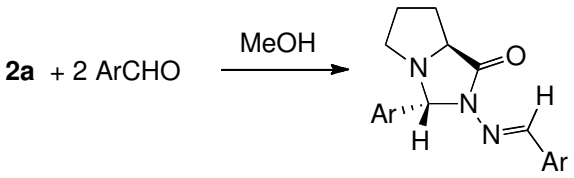
Similarly to aromatic aldehydes, reactions of **2a** and **5** with less reactive cyclohexanone and adamantanone also occurred smoothly at room temperature in MeOH solutions. In all cases the expected hydrazones were obtained in high yields as crystalline materials.

Scheme 4



5 (R = Bn)
2a (R = H)

7a R = Bn, R^1 = H, R^2 = 4-$MeOC_6H_4$
7b R = Bn, R^1 = H, R^2 = 2-Furyl
7c R = Bn, R^1-R^2 = $(CH_2)_5$
7d R = Bn, R^1-R^2 = Adamantyl
7e R = R^1 = H, R^2 = 4-$MeOC_6H_4$
7f R = R^1 = H, R^2 = 4-$NO_2C_6H_4$
7g R = R^1 = H, R^2 = 2-Furyl
7h R = H, R^1-R^2 = $(CH_2)_5$
7i R = H, R^1-R^2 = Adamantyl



8a Ar = 4-$MeOC_6H_4$
8b Ar = 4-$NO_2C_6H_4$
8c Ar = 2-Furyl

Hydrazone **7b** was obtained as a crystalline material suitable for an X-ray crystal structure analysis (Figure 1). The compound in the crystal is enantiomerically pure and the absolute configuration of the molecule has been determined independently by the diffraction experiment. The molecule has the expected *S*-configuration and the C=N bond is (*E*)-configured. The amide group forms an intramolecular hydrogen bond with the ring N-atom to give a loop with a graph set motif[18] of S(5).

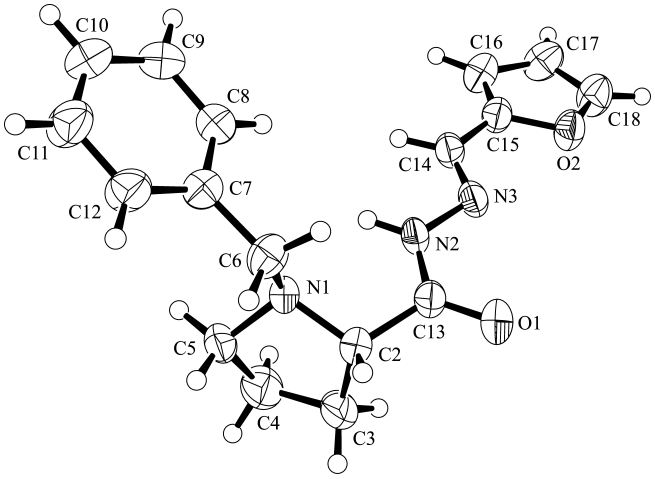
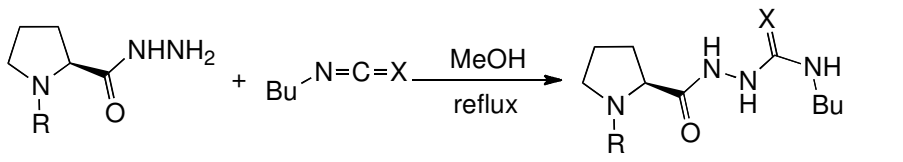


Figure 1. ORTEP plot[17] of the molecular structure of **7b** (arbitrary numbering of the atoms; 50% probability ellipsoids)

Reactions of butyl isocyanate and butyl isothiocyanate with **5** occur smoothly in boiling ethanol yielding the desired semicarbazide **9a** and thiosemicarbazide **9b**, respectively (Scheme 5). On the other hand, treatment of the non-protected **2a** with 1 mol-equivalent of butyl isocyanate and butyl isothiocyanate, respectively, resulted in the formation of the 1:2 adducts **10a** and **10b**, i.e., the products of a two-fold addition, which were obtained along with unconverted starting material **2a**. In another experiment with 2 mol-equivalents of the hetereocumulene, the conversion of **2a** to the corresponding compounds **10** was complete. These results show that these additions occur non-selectively and, remarkably, no 1:1 adduct was obtained regardless of the applied reaction conditions.

Scheme 5

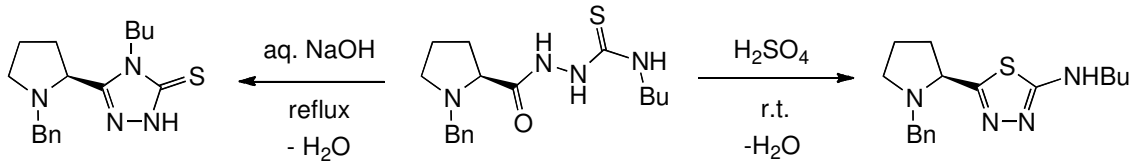


5 (R = Bn)
2a (R = H)

9a R = Bn, X = O
9b R = Bn, X = S
10a R = BuNHCO, X = O
10b R = BuNHCS, X = S

It is well established that thiosemicarbazides derived from carbohydrazides are versatile starting materials for the preparation of diverse heterocycles.[13,15] Thus, heating of **9b** in aqueous NaOH gave the 1,2,4-triazole-3-thione **11**, whereas the reaction in H_2SO_4 at room temperature yielded the 1,3,4-thiadiazol-2-amine derivative **12** (Scheme 6). Further studies aimed at the exploration of proline hydrazides for the preparation of enantiomerically pure bis-heterocyclic products are in progress.

Scheme 6



11 **9b** **12**

3. Conclusions

The present study shows that non-protected (*S*)-proline hydrazide **2a** can be prepared conveniently by using aqueous hydrazine and *N*-benzyl prolinate with subsequent deprotection of the N-atom. Both optically active (*S*)-proline derived hydrazides **2a** and **5** react with aldehydes and cyclic ketones yielding the corresponding hydrazones **7**. However, in the case of the reaction with aldehydes, depending on the reaction conditions, a secondary process leading to a product of type **8** competes with the formation of the corresponding hydrazone. The formation of **8** is rationalized by the cyclocondensation of the initially formed hydrazone **7** with a second molecule of the aldehyde. Furthermore, the reactions of the *N*-benzylated hydrazide **5** with butyl isocyanate and isothiocyanate afforded semicarbazides and thiosemicarbazides, respectively, which are attractive building blocks for the preparation of chiral bis-heterocycles such as 1,3,4-thiadiazoles and 1,2,4-triazol-2-thiones. These compounds and other products derived from **2a** and **5** are of interest as promising organocatalysts and ligands for asymmetric synthesis. Additions of butyl isocyanate and butyl isothiocyanate with the non-protected **2a** occur at both N-atoms in a non-selective manner.

4. Experimental

4.1. General

Melting points were determined in a capillary using a Melt-Temp. II apparatus (Aldrich) or STUART SMP30 and are uncorrected. IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions (ν) in cm^{-1}. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were measured on a Bruker Avance III instrument (600 and 150 MHz, resp.) using solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants *J* in Hz. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker Esquire LC spectrometers. Optical rotations were determined on a *PERKIN-ELMER 241 MC* polarimeter for λ = 589 nm.

4.2. Starting Materials

All solvents and reagents are commercially available and were used as received. Ethyl (*S*)-*N*-benzylprolinate **4** and methyl (*S*)-prolinate **1b** were prepared following a known protocol based on the treatment of the corresponding amino acid, dissolved in ethanol or methanol, with thionyl chloride.[11]

4.3. Synthesis of (*S*)-proline hydrazide 2a

Procedure A: To a magnetically stirred solution of (*S*)-*N*-benzylproline hydrazide **5** (10 mmol) in MeOH (5 ml) was added 10% Pd/C (300 mg). Then, H_2 gas was bubbled through the solution for 24 h; the progress of the reaction was followed by TLC (SiO_2, MeOH/CH_2Cl_2 1:4). After the starting hydrazide was consumed, Pd/C was filtered and the resulting solution was concentrated under reduced pressure. The obtained highly pure product **2a** was analyzed without further purification. Yield: 1.161 g (90%).

Procedure B: To a magnetically stirred solution of (*S*)-*N*-benzylproline hydrazide **5** (5 mmol) in MeOH (10 ml) was added 10% Pd/C (165 mg) and $HCOONH_4$ (5 eq). The mixture was heated to reflux for 1 h. After cooling to r.t., Pd/C was filtered and the resulting solution was concentrated under reduced pressure. The obtained highly pure product **2a** was analyzed without further purification. Yield: 0.121 g (94%). IR (film): ν 3328s (HN), 2976m, 1659vs (C=O), 1541m, 1410m. ^{1}H NMR ($CDCl_3$): δ 8.50

(br. s, HN); 3.74–3.71 (m, CH); 2.95–2.80 (m, 2H); 2.61 (br. s, NH_2); 2.10–2.03 (m, 1H); 1.87–1.82 (m, 1H); 1.70–1.60 (m, 2H). ^{13}C NMR ($CDCl_3$)): δ 175.1 (**C**=O); 59.9 (**C**H); 47.2, 30.6, 26.1 (3 **C**H_2). HR-ESI-MS: 130.0974 (calcd 130.0975 for $C_5H_{12}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = –38 (*c* 1.00, MeOH).

4.4. Synthesis of (*S*)-N-benzylproline hydrazide 5

To a solution of freshly prepared (*S*)-*N*-benzylproline ethyl ester **4** (10 mmol) in MeOH (5 ml) was added $NH_2NH_2 \cdot H_2O$ (20 mmol). The mixture was stirred for 16 h at r.t., and the solvent was evaporated under vacuum. The obtained highly pure product **5** was analyzed without further purification. Yield: 2.102 g (96%). Pale yellow oil. IR (film): ν 3316s (HN), 2969s, 1663vs (C=O), 1496s, 701m. ^{1}H NMR ($CDCl_3$): δ 8.26 (s, HN); 7.32–7.23 (m, 5 arom. H); 3.81, 3.51 (AB, J_{AB} = 13.2, CH_2Ph); 3.28–3.26 (m, CH); 3.02–2.99 (m, 1H); 2.36–2.32 (m, 1H); 2.22–2.18 (m, 1H); 1.89–1.68 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 174.7 (**C**=O); 138.4 (1 arom. C); 128.7, 128.5, 127.3 (5 arom. CH); 66.5 (CH); 60.0 (CH_2Ph); 54.0, 30.6, 24.1 (3 CH_2). HR-ESI-MS: 220.1443 (calcd 220.1444 for $C_{12}H_{18}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 70 (*c* 1.00, MeOH).

4.5. Synthesis of diketopiperazine 6

Procedure A: To a solution of freshly prepared (*S*)-proline methyl ester **1b** (10 mmol) in MeOH (5 ml), was added $NH_2NH_2 \cdot H_2O$ (20 mmol) distilled over KOH pellets. The mixture was stirred for 16 h at r.t., and the solvent was evaporated under vacuum to give **6**. Yield: 1.223 g (63%). Colorless crystals. Mp 140–142 °C; lit.[12b], mp 144–145 °C.

Procedure B: A mixture of (*S*)-proline **1a** (10 mmol) and thionyl chloride (2.4 ml) was heated to reflux for 30 min. After cooling to r.t., an excess of $NH_2NH_2 \cdot H_2O$ (1.18 ml) distilled over KOH pellets was added and the mixture heated to reflux for 1 h. Then, water was added and the aqueous layer was extracted with $CHCl_3$, the organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was passed through a silica gel plug to give **6**. Yield: 0.524 g (27%). Colorless crystals. Mp 139–141 °C.

4.6. General procedure for the synthesis of hydrazones 7a–d

To a stirred solution of a hydrazide **5** (1 mmol) in MeOH (5 ml) at 20 °C, an equimolar quantity of the carbonyl component was added slowly. The mixture was stirred for 16 h at r.t., the solution was concentrated, the resulting solid was treated with Et_2O, filtered, and crystallized from an appropriate solvent.

4.6.1. (2*S*)-1-Benzyl-*N*-[(*E*)-(4-methoxyphenyl)methylidene]pyrrolidine-2-carbohydrazide 7a

Yield: 0.250 g (74%). Colorless crystals. Mp 94–96 °C (EtOH). IR (KBr): ν 3255s (HN), 2973m, 1676vs (C=O), 1603s, 1506m, 1255m. ^{1}H NMR ($CDCl_3$): δ 10.21 (br. s, HN); 7.99 (s, HC=N); 7.71, 6.93 (AA'BB', J_{AB} = 8.3, 4 arom. H); 7.39–7.28 (m, 5 arom. H); 3.93, 3.65 (AB, J_{AB} = 13.2, CH_2Ph); 3.86 (s, MeO); 3.45–3.42 (m, CH); 3.16–3.14 (m, 1H); 2.52–2.47 (m, 1H); 2.35–2.31 (m, 1H); 2.10–1.77 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 170.4 (**C**=O); 148.1 (C=N); 138.4, 130.1, 126.3 (3 arom C); 129.3, 128.7, 128.6, 127.5, 114.1 (9 arom. CH); 67.1 (CH); 60.1 (CH_2Ph); 55.4 (MeO); 54.3, 30.8, 24.3 (3 CH_2). HR-ESI-MS: 338.1865 (calcd 338.1863 for $C_{20}H_{24}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = +104 (*c* 1.00, MeOH).

4.6.2. (2*S*)-1-Benzyl-*N*-[(*E*)-2-furylmethylidene]pyrrolidine-2-carbohydrazide 7b

Yield: 0.232 g (69%). Colorless crystals. Mp 135–136 °C (EtOH). IR (KBr): ν 3250s (HN), 2977m, 1679vs (C=O), 1515m, 1470m, 1346m. ^{1}H NMR ($CDCl_3$): δ 10.22 (br. s, HN); 8.30 (s, HC=N); 7.50, 6.80, 6.47 (3d, *J* = 3.6, 3 furyl H); 7.35–7.25 (m, 5 arom. H); 3.89, 3.61 (AB, J_{AB} = 13.2, CH_2Ph); 3.40–3.37 (m, CH); 3.11–3.08 (m, 1H); 2.47–2.43 (m, 1H); 2.30–2.27 (m, 1H); 2.04–1.76 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 170.8 (**C**=O); 149.4, 138.2 (2 arom. C); 138.8 (C=N); 144.6, 128.7, 128.6, 127.6, 113.1, 111.9 (8 arom. CH); 67.1 (CH); 60.1 (CH_2Ph); 54.2, 30.8, 24.3 (3 CH_2). HR-ESI-MS: 298.1550 (calcd 298.1550 for $C_{17}H_{20}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = +121 (*c* 1.00, MeOH).

4.6.3. (2*S*)-1-Benzyl-*N*-(cyclohexylidene)pyrrolidine-2-carbohydrazide 7c

Yield: 0.269 g (81%). Colorless crystals. Mp 85–87 °C (EtOH). IR (KBr): ν 3198s (HN), 2933s, 1678vs (C=O), 1550m, 1209m, 741m. ^{1}H NMR ($CDCl_3$): δ 10.15 (br. s, HN); 7.33–7.27 (m, 5 arom. H); 3.91, 3.56 (AB, J_{AB} = 13.2, CH_2Ph); 3.41–3.39 (m, CH); 3.12–3.09 (m, 1 proline H); 2.44–1.62 (m, 5 proline H, 10 cyclohexyl H). ^{13}C

NMR ($CDCl_3$): δ 170.2 (**C**=O); 161.0 (C=N); 138.6 (1 arom C); 128.7, 128.6, 127.4 (5 arom. CH); 67.4 (CH); 60.2 (CH_2Ph); 54.3, 35.5, 30.8, 25.8, 26.7, 25.9, 25.6, 24.3 (3 proline CH_2, 5 cyclohexyl CH_2). HR-ESI-MS: 300.2070 (calcd 300.2070 for $C_{18}H_{26}N_3O$, $[M+1]^+$).). $[\alpha]_D^{25}$ = –102 (*c* 1.00, MeOH).

4.6.4. (2*S*)-*N*-(2-Adamantylidene)-1-benzylpyrrolidine-2-carbohydrazide 7d

Yield: 0.263 g (75%). Colorless crystals. Mp 169–171 °C (EtOH). IR (KBr): ν 3203s (HN), 2912s, 1666vs (C=O), 1553m, 1210m, 741m. ^{1}H NMR ($CDCl_3$): δ 10.17 (br. s, HN); 7.33–7.24 (m, 5 arom. H); 3.92, 3.53 (AB, J_{AB} = 13.2, CH_2Ph); 3.42–3.39 (m, CH); 3.10–3.08 (m, 1 proline H); 2.92, 2.82 (2 br. s, 2 adamantyl CH); 2.42–2.28 (m, 2 proline H); 2.05–1.73 (m, 3 proline H, 12 adamantyl H). ^{13}C NMR ($CDCl_3$): δ 170.3 (C=O); 167.4 (C=N); 138.7 (1 arom. C); 128.6, 128.4, 127.4 (5 arom. CH); 67.5 (CH); 60.2 (CH_2Ph); 54.3, 39.5, 39.0, 37.8, 36.3, 31.5, 30.7, 27.8, 24.4 (3 proline CH_2, 9 adamantyl C). HR-ESI-MS: 352.2382 (calcd 352.2383 for $C_{22}H_{30}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = –74 (*c* 1.00, $CHCl_3$).

4.7. General procedure for the synthesis of hydrazones 7e–i

To a stirred solution of a hydrazide **5** (1 mmol) in MeOH (5 ml) at 20 °C, an equimolar quantity of the carbonyl component in MeOH (10 ml) was added during 4 h. The mixture was stirred for 16 h at r.t., the solution was concentrated, the resulting solid was treated with Et_2O and filtered.

4.7.1. (2*S*)-*N*-[(*E*)-(4-Methoxyphenyl)methylidene]pyrrolidine-2-carbohydrazide 7e

Yield: 0.188 g (76%). Colorless crystals. Mp 85–86 °C (Et_2O). IR (KBr): ν 3257s (HN), 2965m, 1686vs (C=O), 1607s, 1513m, 1253s. ^{1}H NMR ($CDCl_3$): *major isomer*: δ 8.12 (s, HC=N); 7.35, 6.70 (AA'BB', J_{AB} = 8.3, 4 arom. H); 4.93–4.91 (m, CH); 3.76 (s, MeO); 3.70–3.61 (m, 2 proline H); 2.49–2.08 (m, 4 proline H); *minor isomer*: δ 8.18 (s, HC=N); 7.67 6.88 (AA'BB', J_{AB} = 8.3, 4 arom. H); 4.17–4.13 (m, CH); 3.82 (s, MeO); 3.20–3.06 (m, 2 proline H); 2.39–1.80 (m, 4 proline H). ^{13}C NMR ($CDCl_3$): *major isomer*: δ 161.3 (C=O); 146.7 (C=N); 142.4, 126.2, (2 arom. C); 129.3 114.0 (4 arom. CH); 58.6 (CH); 55.2 (MeO); 46.6, 30.7, 24.6 (3 CH_2); *minor isomer*: δ 161.7 (C=O); 148.9 (C=N); 142.4, 126.2 (2 arom. C); 128.8, 114.1 (4 arom. CH); 59.9

(CH); 55.3 (MeO); 46.6, 29.8, 24.6 (3 CH_2). HR-ESI-MS: 248.1392 (calcd 248.1394 for $C_{13}H_{18}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = –65 (*c* 1.00, MeOH).

4.7.2. (2*S*)-*N*-[(*E*)-(4-Nitrophenyl)methylidene]pyrrolidine-2-carbohydrazide 7f

Yield: 0.233 g (89%). Yellow solid. Mp 264–268 °C (Et_2O). IR (KBr): ν 3074m, 2965m, 1694vs (C=O), 1518m, 1342s. ^{1}H NMR ((D$_6$)DMSO): *major isomer*: δ 8.21 (s, HC=N); 8.28, 8.00 (AA'BB', J_{AB} = 8.6, 4 arom. H); 4.86–4.83 (m, CH); 3.37–3.17 (m, 2 proline H); 2.55–1.91 (m, 4 proline H); *minor isomer*: δ 8.44 (s, HC=N); 8.30, 7.97 (AA'BB', J_{AB} = 8.6, 4 arom. H); 4.21–4.19 (m, CH); 3.17–3.07 (m, 2 proline H); 2.34–1.91 (m, 4 proline H). ^{13}C NMR ((D$_6$)DMSO): *major isomer*: δ 170.7, (C=O); 143.7 (C=N); 148.5, 140.4 (2 arom. C); 128.6, 124.5 (4 arom. CH); 58.4 (CH); 46.2, 29.3, 24.1 (3 CH_2); *minor isomer*: δ 166.4 (C=O); 146.5 (C=N); 148.5, 140.6 (2 arom. C); 128.6, 124.4 (4 arom. CH); 59.0 (CH); 46.1, 30.0, 24.3 (3 CH_2). HR-ESI-MS: 263.1137 (calcd 263.1139 for $C_{12}H_{15}N_4O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 57 (*c* 1.00, MeOH).

4.7.3. (2*S*)-*N*-[(*E*)-2-Furylmethylidene]pyrrolidine-2-carbohydrazide 7g

Yield: 0.164 g (79%). Colorless crystals. Mp 79–81 °C (Et_2O). IR (KBr): ν 3112s (HN), 2977m, 1690vs (C=O), 1625m, 1231m. ^{1}H NMR ($CDCl_3$): *major isomer*: δ 8.13 (s, HC=N); 7.34, 6.54, 6.33 (3d, *J* = 3.7, 3 furyl H); 4.92–4.89, (m, CH); 3.70–3.46 (m, 2 proline H); 2.25–2.09 (m, 4 proline H); *minor isomer*: δ 8.31 (s, HC=N); 7.48, 6.68, 6.42 (3d, *J* = 3.7, 3 furyl H); 4.62–4.59 (m, CH); 3.57–3.36 (m, 2 proline H); 2.55–1.90 (m, 4 proline H). ^{13}C NMR ($CDCl_3$): *major isomer*: δ 170.3 (C=O); 148.9 (1 arom. C); 144.4, 113.9, 111.7 (3 furyl CH); 136.5 (C=N); 58.8 (CH); 46.4, 29.5, 24.4 (3 CH_2); *minor isomer*: δ 170.3 (C=O); 149.0 (1 arom. C); 144.8, 113.9, 112.0 (3 furyl CH); 139.3 (C=N); 59.5 (CH); 46.8, 30.4, 24.7 (3 CH_2). HR-ESI-MS: 208.1077 (calcd 208.1081 for $C_{10}H_{14}N_3O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = –80 (*c* 1.00, MeOH).

4.7.4. (2*S*)-*N*-(Cyclohexylidene)pyrrolidine-2-carbohydrazide 7h

Yield: 0.082 g (39%). IR (film): ν 3261s (HN), 2935s, 1683vs (C=O), 1534m, 1221m, 1043m. ^{1}H NMR ((D$_6$)DMSO): *major isomer*: δ 10.96 (br. s, HN); 4.09–4.06 (m, CH); 3.27–3.17 (m, 2 proline H); 2.46–1.53 (m, 5 proline H, 10 cyclohexyl H); *minor isomer*: δ 11.10 (br. s, HN); 4.65–4.62 (m, CH); 3.27–3.17 (m, 2 proline H); 2.46–1.53 (m, 5 proline H, 10 cyclohexyl H). ^{13}C NMR ((D$_6$)DMSO): *major isomer*: δ

170.5, 167.7 (C=O, C=N); 58.2 (CH); 45.8, 35.4, 30.0, 29.2, 27.3, 26.1, 25.4, 24.0 (3 proline CH_2, 5 cyclohexyl CH_2); *minor isomer*: δ 170.5, 165.4 (C=O, C=N); 58.5 (CH); 46.0, 35.6, 30.4, 29.3, 27.4, 26.2, 25.5, 24.1 (3 proline CH_2, 5 cyclohexyl CH_2). HR-ESI-MS: 210.1598 (calcd 210.1601 for $C_{11}H_{20}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 88 (*c* 1.00, MeOH).

4.7.5. (2*S*)-*N*-(2-Adamantylidene)pyrrolidine-2-carbohydrazide 7i

Yield: 0.104 g (40%). Colorless crystals. Mp 95–97 °C (Et_2O). IR (KBr): ν 3127s (HN), 2915s, 1686vs (C=O), 1542m, 1450m, 1226m. ^{1}H NMR ((D_6)DMSO): *major isomer*: δ 11.03 (br. s, HN); 4.31–4.28 (m, CH); 3.25–3.13 (m, 2 proline H); 2.55, 2.49 (2 br. s, 2 adamantyl CH); 2.00–1.65 (m, 4 proline H, 12 adamantyl H); *minor isomer*: δ 10.94 (br. s, HN); 4.65–4.62 (m, CH); 2.55, 2.49 (2 br. s, 2 adamantyl CH); 2.41–2.25 (m, 2 proline H); 2.00–1.65 (m, 4 proline H, 12 adamantyl H). ^{13}C NMR ((D_6)DMSO): *major isomer*: δ 169.9, 166.1 (C=O, C=N); 58.7 (CH); 46.2, 39.2, 39.0, 37.8, 36.2, 31.9, 29.4, 27.6, 24.4 (3 proline CH_2, 5 adamantyl CH_2 and 4 adamantyl CH); *minor isomer*: δ 170.6, 166.2 (C=O, C=N); 58.4 (CH); 46.0, 39.0, 38.8, 37.6, 36.1, 31.2, 29.3, 27.5, 24.3 (3 proline CH_2, 5 adamantyl CH_2, 4 adamantyl CH). HR-ESI-MS: 262.1912 (calcd 262.1914 for $C_{15}H_{24}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 63 (*c* 1.00, MeOH).

4.8. General procedure for the synthesis of compounds 8

To a stirred solution of an aldehyde (2 mmol) in EtOH (5 mL), a solution of **2a** (1 mmol) in EtOH (5 mL) was added dropwise at room temperature. The mixture was stirred overnight, and then the solvent was removed under reducer pressure. Crude product **8** was purified by crystallization or flash chromatography.

4.8.1. (7a*S*)-3-(4-Methoxyphenyl)-2-{[(*Z*)-(4-methoxyphenyl)methyliden]amino} hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one 8a

Yield: 0.186 g (72%). Colorless oil (flash chromatography, hexane/AcOEt, 1:1) (lit.[8a], mp 110–112 °C). IR (KBr): ν 3436br, 2963m, 2936m, 1713vs (C=O), 1608s, 1514s, 1251s. ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 1H, CH=N); 7.61, 6.88 (AA'BB', J_{AB} = 8.82, 4 arom. H); 7.30, 6.93 (AA'BB', J_{AB} = 8.67, 4 arom. H); 5.55 (s, 1H, HC(6)); 4.04–4.00 (m, 1H, HC(5)); 3.46–3.40 (m, 1H, HC(2)); 2.90–2.85 (m, 1H, HC(2)); 2.24–

2.16 (m, 2H, HC(4)); 1.95–1.86 (m, 2H, HC(3)). ^{13}C NMR ($CDCl_3$): δ 172.1 (C=O); 161.8, 160.1, 132.2, 127.1 (4 arom. C); 149.9 (C=N); 129.4, 127.7, 114.7, 114.2 (8 arom. CH); 82.4 (C(6)); 63.3 (CH); 55.5 (2 MeO); 56.3, 27.7, 25.1 (3 proline CH_2). HR-ESI-MS: 366.1810 (calcd 366.1812 for $C_{21}H_{24}N_3O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 75 (*c* 1.00, CH_2Cl_2).

4.8.2. (7a*S*)-3-(4-Nitrophenyl)-2-{[(*Z*)-(4-nitrophenyl)methyliden]amino} hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one 8b

Yield: 0.216 g (79%). Pale yellow crystals. Mp 144–145°C (Et_2O). IR (KBr): ν 3421br, 2954w, 2877w, 1714vs (C=O), 1522s, 1344s. ^{1}H NMR ($CDCl_3$): δ 9.27 (s, 1H, CH=N); 8.26, 7.77 (AA'BB', J_{AB} = 9.00, 4 arom. H); 8.21, 7.62 (AA'BB', J_{AB} = 9.00, 4 arom. H); 5.63 (s, 1H, HC(6)); 4.04–4.00 (m, 1H, HC(5)); 3.46–3.41 (m, 1H, HC(2)); 2.98–2.92 (m, 1H, HC(2)); 2.31–2.23 (m, 1H, HC(4)); 2.21–2.15 (m, 1H, HC(4)); 1.98–1.89 (m, 2H, HC(3)). ^{13}C NMR ($CDCl_3$): δ 172.3 (C=O); 149.5 (C=N); 149.1, 148.4, 146.2, 140.4 (4 arom. C); 128.2, 128.0, 124.3, 124.2 (8 arom. CH); 83.24 (C(6)); 63.99 (CH); 56.40, 28.29, 25.21 (3 proline CH_2). HR-ESI-MS: 396.1299 (calcd 396.1303 for $C_{19}H_{18}N_5O_5$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 51 (*c* 1.00, CH_2Cl_2).

4.8.3. (7a*S*)-3-(Furan-2-yl)-2-{[(*Z*)-furan-2-ylmethyliden]amino}hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one 8c

Yield: 0.151 g (69%). Colorless crystals. Mp 184–186°C (Et_2O); lit.[8b], mp 183–185 °C. IR (KBr): ν 3436br, 3112w, 2973w, 2880w, 1700vs (C=O), 1403m, 1382m, 1335m. ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 1H, CH=N), 7.53–7.48 (m, 1 furyl H); 7.43–7.39 (m, 1 furyl H); 6.78–6.74 (m, 1 furyl H); 6.47–6.43 (m, 1 furyl H); 6.39–6.32 (m, 2 furyl H); 5.61 (s, 1H, HC(6)); 4.12–4.07 (m, 1H, HC(5)); 3.45–3.40 (m, 1H, HC(2)); 2.85–2.79 (m, 1H, HC(2)); 2.25–2.12 (m, 2H, HC(4)); 1.92–1.86 (m, 2H, HC(3)). ^{13}C NMR ($CDCl_3$): δ 172.1 (C=O); 151.4, 149.7 (2 furyl C); 145.1, 143.4 (2 furyl CH); 140.8 (C=N); 114.6, 112.2, 110.6, 108.4 (4 furyl CH); 77.3 (C(6)); 64.1 (CH); 55.76, 27.57, 25.09 (3 proline CH_2). HR-ESI-MS: 286.1186 (calcd 286.1186 for $C_{15}H_{16}N_3O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = –193 (*c* 0.44, CH_2Cl_2).

4.9. General procedure for the synthesis of compounds 9a–b

A mixture of **5** (1 mmol) and butyl isocyanate or isothiocyanate (1.1 mmol) in EtOH (5 ml) was heated to reflux for 2 h. The formed product was then filtered off and washed with Et_2O.

4.9.1. 1-{[(2*S*)-1-Benzylpyrrolidine-2-carbonyl]amino}-3-methylurea 9a

Yield: 0.312 g (98%). Colorless crystals. Mp 85–88 °C (MeOH). IR (KBr): ν 3390s, 3277s (HN), 2958s, 1686vs (C=O), 1671vs (C=O), 1565s, 1254m, 704m. ^{1}H-NMR ($CDCl_3$): δ 9.04 (br. s, HN); 7.34–7.25 (m, 5 arom. H); 5.29 (br. s, HN); 3.90, 3.58 (AB, J_{AB} = 13.2, CH_2Ph); 3.34–3.31 (m, CH); 3.19–3.15 (m, butyl CH_2); 3.08–3.06 (m, 1 proline H); 2.42–2.40 (m, 1 proline H); 2.22–2.20 (m, 1 proline H); 1.97–1.78 (m, 3 proline H); 1.45–1.41, 1.33–1.30 (2m, 2 butyl CH_2); 0.90 (t, J = 7.8, butyl Me). ^{13}C NMR ($CDCl_3$): δ 173.5, 157.6 (2 **C**=O); 138.2 (1 arom. C); 129.0, 128.6, 127.5 (5 arom. CH); 66.4 (CH); 60.1 (CH_2Ph); 54.2, 30.6, 24.2 (3 proline CH_2); 39.9, 32.1, 19.9 (3 butyl CH_2); 13.7 (butyl Me). HR-ESI-MS: 319.2131 (calcd 319.2129 for $C_{17}H_{27}N_4O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = –18 (*c* 1.00, $CHCl_3$).

4.9.2. 1-{[(2*S*)-1-Benzylpyrrolidine-2-carbonyl]amino}-3-methylthiourea 9b

Yield: 0.272 g (93%). Pale yellow oil. IR (film): ν 3307br. s (HN), 2930s, 1683vs (C=O), 1540s, 1455m, 1273m. ^{1}H NMR ($CDCl_3$): δ 9.41 (br. s, HN); 7.44–7.25 (m, 5 arom. H); 7.01 (br. s, HN); 3.98, 3.59 (AB, J_{AB} = 13.2, CH_2Ph); 3.56–3.53 (m, butyl CH_2); 3.35–3.32 (m, CH); 3.11–3.09 (m, 1 proline H); 2.44–2.41 (m, 1 proline H); 2.23–2.20 (m, 1 proline H); 2.00–1.80 (m, 3 proline H); 1.58–1.53, 1.41–1.23 (2m, 2 butyl CH_2); 0.94 (t, J = 7.8, butyl Me). ^{13}C NMR ($CDCl_3$): δ 180.3 (C=S); 170.6 (C=O); 137.9 (1 arom. C); 129.2, 128.5, 127.5 (5 arom. CH); 66.2 (CH); 60.3 (CH_2Ph); 54.1, 30.7, 24.2 (3 proline CH_2); 44.6, 31.1, 20.1 (3 butyl CH_2); 13.8 (butyl Me). HR-ESI-MS: 335.1899 (calcd 335.1900 for $C_{17}H_{27}N_4OS$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 68 (*c* 1.00, $CHCl_3$).

4.10. General procedure for the synthesis of compounds 10a–b

A mixture of **2a** (1 mmol) and butyl isocyanate or isothiocyanate (2.1 mmol) in EtOH (5 ml) was heated to reflux for 2 h. The formed product was then filtered off, washed with Et_2O, and crystallized from H_2O.

4.10.1. 1-Butyl-3-{[(2*S*)-1-(butylcarbamoyl)pyrrolidine-2-carbonyl]amino}urea 10a

Yield: 0.173 g (76%). Colorless crystals. Mp 80–82 °C (H_2O). IR (KBr): ν 3297s (HN), 2958s, 1674vs (C=O), 1550s, 1364m. ^{1}H NMR ((D$_6$)DMSO): δ 9.64 (br. s, HN); 7.62, 6.62, 6.28 (3s, 3 HN); 4.05–4.03 (m, CH); 3.34–3.24 (m, proline CH_2); 3.04–2.95 (m, 2 butyl CH_2); 2.01–1.74 (m, 2 proline CH_2); 1.41–1.36, 1.29–1.24 (2m, 4 butyl CH_2); 0.88–0.84 (m, 2 butyl Me). ^{13}C NMR ((D$_6$)DMSO): δ 173.4, 158.8, 157.2 (3 C=O); 59.2 (CH); 46.3, 29.6, 25.0 (3 proline CH_2); 40.6, 40.1, 32.6, 32.1, 20.1, 20.0 (6 butyl CH_2); 14.2, 14.1 (2 butyl Me). HR-ESI-MS: 350.2162 (calcd 350.2163 for $C_{15}H_{29}N_5NaO_3$, [*M*+Na]$^+$). $[\alpha]_D^{25}$ = – 11 (*c* 1.00, MeOH).

4.10.2. 1-Butyl-3-{[(2*S*)-1-(butylthiocarbamoyl)pyrrolidine-2-carbonyl]amino} thiourea 10b

Yield: 0.289 g (78%). Colorless crystals. Mp 178–182 °C (H_2O). IR (KBr): ν 3254s (HN), 2956s, 1676vs (C=O), 1546s, 1377m, 1189m. ^{1}H NMR ((D$_6$)DMSO): δ 9.97 (br. s, HN); 9.18, 7.70, 7.53 (3s, 3 HN); 4.66–4.64 (m, CH); 3.60–3.34 (m, proline CH_2, 2 butyl CH_2); 2.15–1.80 (m, 2 proline CH_2); 1.55–1.46, 1.32–1.25 (2m, 4 butyl CH_2); 0.90–0.85 (m, 2 butyl Me). ^{13}C NMR ((D$_6$)DMSO): δ 178.9, 173.8, 171.7 (2 C=S, C=O); 64.2 (CH); 48.6, 29.6, 24.5 (3 proline CH_2); 45.2, 43.8, 31.5, 31.2, 20.0, 19.9 (6 butyl CH_2); 14.3, 14.2 (2 butyl Me). HR-ESI-MS: 382.1701 (calcd 382.1706 for $C_{15}H_{29}N_5NaOS_2$, [*M*+Na]$^+$). $[\alpha]_D^{25}$ = – 54 (*c* 1.00, MeOH).

4.11. Synthesis of 1,2,4-triazole-3-thione 11

A mixture of **9b** (1 mmol) and a 2% aqueous solution of NaOH (5 ml) was heated to reflux for 2 h. Then, the mixture was neutralized with AcOH, and the formed precipitate was filtered off and crystallized from MeOH. Yield: 0.225 g (67%). Colorless crystals. Mp 135–136 °C (MeOH). IR (KBr): ν 3258br. m (HN), 2964s, 2533br. m, 1569s, 1455m, 1359m, 1297m. ^{1}H NMR ($CDCl_3$): δ 10.31 (br. s, HN); 7.30–7.21 (m, 5 arom. H); 4.23–3.81 (m, butyl CH_2); 3.81, 3.43 (AB, J_{AB} = 13.2, CH_2Ph); 3.80–3.72 (m, CH); 3.44–3.13 (m, proline CH_2); 2.41–1.85 (m, 2 proline CH_2); 1.72–1.32 (m, 2 butyl CH_2); 0.96 (t, *J* = 7.8, butyl Me). ^{13}C NMR ($CDCl_3$): δ 161.2 (C=S); 142.6, 137.8 (triazole C(3), arom. C); 128.8, 128.3, 127.6 (5 arom. CH); 60.1 (CH); 58.2 (CH_2Ph); 53.2, 30.2, 23.0 (3 proline CH_2); 44.4, 33.2, 20.3 (3 butyl CH_2); 13.6

(butyl Me). HR-ESI-MS: 317.1794 (calcd 317.1794 for $C_{17}H_{25}N_4S$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 126 (*c* 1.00, $CHCl_3$).

4.12. Synthesis of 1,3,4-thiadiazol-2-amine (12)

A solution of **9b** (1 mmol) in 5 ml conc. H_2SO_4 was kept at r.t. for 1 d. After neutralization of the mixture with aqueous NH_4OH, the solid product was filtered off, dried, and crystallized from MeOH. Yield: 0.177 g (56%). Yellowish crystals. Mp 99–100 °C (MeOH). IR (KBr): ν 3242s (HN), 2953s, 1537s, 1478m, 737m. ^{1}H NMR ($CDCl_3$): δ 7.33–7.24 (m, 5 arom. H); 5.27 (br. s, HN); 4.02, 3.95 (AB, J_{AB} = 13.2, CH_2Ph); 3.98–3.96 (m, CH); 3.34–3.31 (m, butyl CH_2); 3.07–3.04 (m, 1 proline H); 2.36–2.31 (m, 2 proline H); 1.92–1.81 (m, 3 proline H); 1.68–1.63, 1.46–1.43 (2m, 2 butyl CH_2); 0.96 (t, *J* = 7.8, butyl Me). ^{13}C NMR ($CDC1_3$): δ 170.8, 144.9 (thiadiazol C(2), C(5)); 139.2 (1 arom. C); 128.8, 128.3, 127.2 (5 arom. CH); 63.7 (CH); 58.0 (CH_2Ph); 53.0, 33.3, 22.9 (3 proline CH_2); 47.0, 31.5, 20.0 (3 butyl CH_2); 13.7 (butyl Me). HR-ESI-MS: 317.1794 (calcd 317.1794 for $C_{17}H_{25}N_4S$, $[M+1]^+$). $[\alpha]_D^{25}$ = – 92 (*c* 1.00, $CHCl_3$).

4.13. X-Ray crystal-structure determination of 7b

All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer[19] using CuK_α radiation (λ = 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. The data collection and refinement parameters are given below[20] and a view of the molecule is shown in Figure 1. Data reduction was performed with *CrysAlisPro*.[19] The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[19] was applied. Equivalent reflections, other than Friedel pairs, were merged. The structure was solved by direct methods using *SHELXS97*,[21] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. The amine H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed

isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimised the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. Refinement of the absolute structure parameter[22] yielded a value of –0.0(2), while the Hooft analysis[23] gave y = 0.07(5), $P2$ = 1.000 and $P3$ = 0.000, which confidently confirms that the refined coordinates represent the true enantiomorph. Neutral atom scattering factors for non-H-atoms were taken from ref.[24], and the scattering factors for H-atoms were taken from ref.[25] Anomalous dispersion effects were included in F_c;[26] the values for f' and f'' were those of ref.[27] The values of the mass attenuation coefficients are those of ref.[28] All calculations were performed using the *SHELXL97*[21] program.

Crystal data for **7b**: $C_{17}H_{19}N_3O_2$, M = 297.36, crystallised from isopropanol, colourless, prism, crystal dimensions 0.15 × 0.22 × 0.25 mm, monoclinic, space group $P2_1$, Z = 2, reflections for cell determination 6644, 2θ range for cell determination 6 – 153°, a = 5.54324(6) Å, b = 10.11476(12) Å, c = 14.24604(17) Å, β = 97.5394(11), V = 791.849(16) Å^3, T = 160(1) K, D_X = 1.247 g·cm^{-3}, μ(CuK_α) = 0.675 mm^{-1}, scan type ω, $2\theta_{(max)}$ = 153.5°, transmission factors (min; max) = 0.887; 1.000, total reflections measured 8322, symmetry independent reflections 3035, reflections with $I > 2\sigma(I)$ 2996, reflections used in refinement 3035, parameters refined 203, restraints 1; $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0286, $wR(F^2)$ [all data] = 0.0800 ($w = [\sigma^2(F_o^2)+ (0.0511P)^2+0.0771P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.034, final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.15; –0.10 e Å^{-3}.

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